

Medical Staff Conference

Acute Leukemia

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. DONALD A. YOUNG:* This is the third University of California Hospital admission for this 32-year-old man, a graduate student from Berkeley, who was admitted because of vomiting, weakness and malaise. The patient was in good health until May 1965 when he had onset of what he referred to as a cold with general malaise and fatigue. This continued and in June 1965, because of intermittent fever and cough, he sought medical attention at another hospital. A diagnosis of acute leukemia was made on examination of bone marrow aspirate and he was referred here for further evaluation. He was here from 16 June to 29 June 1965. Therapy was begun with prednisone and then with 6-mercaptopurine; and later, because of a positive reaction to a skin test for tuberculosis, isoniazid was added to the therapeutic regimen. The patient became febrile. *Salmonella montevideo* grew on cultures of stool and sputum. Sputum and gastric cultures were negative for acid-fast bacilli. He was treated with a large number of antibiotics during his stay in hospital. Three days after he was discharged he was readmitted because of recurrent fever, cough, diaphoresis and malaise. He was found to have pneumonia. During the second stay in hospital the number of leukocytes decreased from 83,000 per cu mm of blood to 900. Platelet count, however, remained normal and the bone marrow continued to show leukemic cells. Discharged after a month in hospital, he was readmitted not quite three weeks later because of persistent nausea, vomiting, cough, fatigue, malaise and a very low hematocrit.

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On physical examination he seemed to be in no acute distress. There were no petechiae noted in the skin but there were flame hemorrhages in the fundi of both eyes. There were no palpable lymph nodes. Dullness was noted at the base of the right lung and fremitus and breath sounds were decreased. The liver and spleen were not enlarged.

Laboratory data at the time of this admission: Leukocytes, 600 per cu mm; packed red cell volume, 17 per cent; hemoglobin, 9.7 per 100 ml; platelet count (as in preceding two months) remained in the 100,000-250,000 range, and cultures again showed *Salmonella montevideo* in sputum and stool. Numerous blood and urine cultures were negative for pathogenic organisms.

DR. LLOYD H. SMITH, JR.:† This patient was referred to us by Dr. Gilbert Roberts.

DR. GILBERT ROBERTS: When he was admitted to the hospital, he had a mediastinal mass, right pleural effusion, and enlargement of cervical lymph nodes on the right side. Our diagnosis was Hodgkin's disease, not leukemia. Biopsy was done and the diagnosis was established by marrow aspiration.

Dr. Smith: I believe there are x-rays to be seen.

Roentgenographic Features

DR. WARREN RUSSELL‡: The x-ray films present a rather interesting chronology of the patient's course. The first film of the chest, taken 17 June, shows a very pronounced widening of the mediastinum and a rather faint infiltrate extending out to

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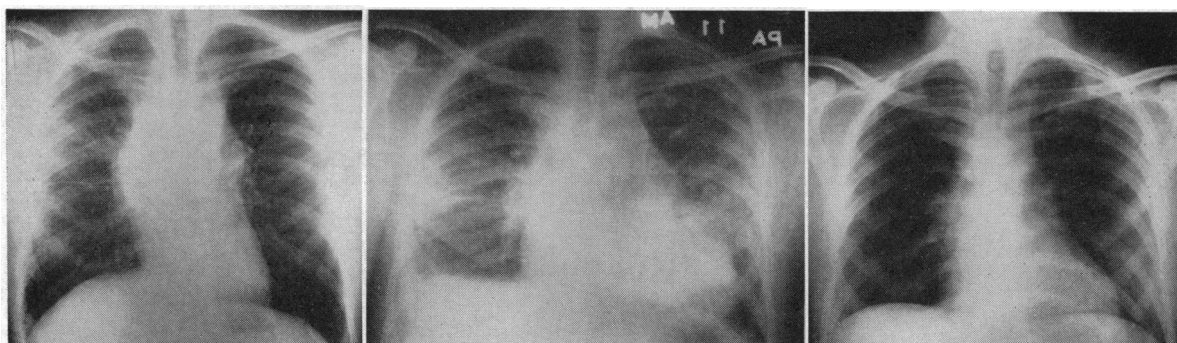


Figure 1.—Film at left, taken 17 June, shows pronounced widening of the mediastinum and faint infiltrate extending out to lung fields. Center film, 23 July, shows progression to bilateral pulmonary infiltrates. A film taken 3 September (right frame) shows considerable regression of radiographic abnormalities—the lung fields essentially clear and the mediastinum not as wide as it had been for two and a half months earlier.

the lung fields. By July this had progressed to bilateral pulmonary infiltrates. The most recent film, 3 September, shows decided regression of the radiographic abnormalities, with lung fields essentially clear and the mediastinum, although still wide, much less so than at first (See Figure 1).

Dr. Smith: Thank you, Dr. Russell. The patient is not being presented this morning because of the degree of his illness. The discussion will be led by Dr. Bruce Lewis§ and Dr. Martin Cline.¶

Clinical Manifestations

DR. BRUCE F. LEWIS: Acute leukemia—"suppuration of the blood," as it was called by Bennett in 1845—comes to clinical notice in a variety of ways. The patient that Dr. Young presented is a rather typical example of adults with acute myeloblastic leukemia. As is the rule in this disease, the patient has not responded to therapy. He has had a variety of complications mostly of an infectious nature, and it appears that the disease is progressing inexorably.

We could have presented a different patient this morning—for example, a woman 23 years of age, whom we have observed periodically over the last nine months or so. Newly married, she came to the hospital for the first time shortly after her honeymoon because of persistent fever, weakness and a high leukocyte count. As it turned out, she had acute lymphoblastic leukemia. After treatment with corticosteroids, she had a very rapid remission of disease; and on a program of alternating 6-mercaptopurine and methotrexate, it has been in remission ever since. In the course of the disease central nervous system leukemia (which I shall discuss later) developed. This condition

which we have come to consider an expected feature of lymphoblastic leukemia, was successfully treated and the patient is continuing to do well. Thus, there are basically two types of acute leukemia: on the one hand, acute myeloblastic and monoblastic leukemia, which are clinically very similar; and on the other hand, acute lymphoblastic leukemia. In contrast to acute myeloblastic leukemia, acute lymphoblastic leukemia usually responds to therapy, at least initially, and has a somewhat more benign course. Since treatment for the two diseases is different, it is important to make an accurate morphological diagnosis.

There are other clinical syndromes that are seen in leukemia. For example, a number of older persons have been described who have anemia, chronic unexplained leukopenia, or thrombocytopenia. Eventually after a period which may run for several years, the typical features of acute myelogenous leukemia develop and the typical course of that disease ensues.

Acute lymphocytic leukemia is somewhat more common than the combination of acute myelocytic and acute monocytic leukemia. In all forms of acute leukemia male patients outnumber females about three to two. Most of the patients with acute lymphocytic leukemia are of the pediatric age group, and there is a sharp peak in the incidence of acute lymphocytic leukemia at about the age of three. After that age, the incidence of lymphocytic leukemia falls off sharply. As the incidence of granulocytic and monocytic leukemia does not change appreciably during life, these forms of acute leukemia are the most common in the elderly.

The signs and symptoms of leukemia can be related to just a few factors: leukemic proliferation of the marrow, leukemic infiltration of other or-

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gans and poorly understood metabolic alterations. As a result of leukemic proliferation in the marrow, deficiencies develop in production of red cells, white cells and platelets, leading to the familiar problems of anemia, bleeding and infections. Leukemic infiltration of other organs result in hepatosplenomegaly or lymphadenopathy or both. Since any organ can be infiltrated by leukemia, a variety of symptoms may result. Metabolic alterations may cause symptoms such as weakness, lassitude or fever which cannot be adequately explained.

Physical findings in acute leukemia can also be related to these same factors. An important finding is sternal tenderness, which can be present in as many as two-thirds of patients with acute leukemia. It has been pointed out that patients who have sternal tenderness tend to do somewhat less well than patients who have not. Lymphadenopathy and hepatosplenomegaly are common, being somewhat more common in the lymphoblastic form of leukemia than in the myeloblastic or monocytic forms. Skin infections are particularly common in myeloblastic leukemia, and infiltration of the gums is common in monoblastic leukemia. However, in all forms of leukemia a variety of skin manifestations can be present, frequently due to leukemic infiltration of the skin. Hemorrhagic phenomena of all sorts occur with leukemia, including petechiae, purpura and ecchymoses. There may be evidence of bleeding from any site.

So far as diagnosis of acute leukemia is concerned, this is almost exclusively morphologic at the moment. It is a diagnosis which is usually considerably simpler for the hematologist studying the living patient than for the pathologist at autopsy. The reasons for this are multiple. Very few patients with acute leukemia die without having had treatment, and treatment may erase all the manifestations including marrow and organ infiltration. In addition, recently there have been reports of patients with typical acute leukemia who died without receiving cytotoxic therapy, and who had no evidence of organ and marrow infiltration at autopsy. In life, the diagnosis can usually be made from the peripheral blood. About 60 per cent of patients with acute leukemia have high leukocyte counts. Forty per cent have low or normal counts. In some cases, no abnormal cells will be found in the peripheral blood; then the diagnosis can be made only by examination of the bone marrow. Classically, the bone marrow in acute leukemia is

densely infiltrated with immature leukemic cells. A variety of clues may enable differentiation between lymphoblastic and myeloblastic leukemia. The presence of granules in developing cells, particularly peroxidase-positive granules, indicates a diagnosis of either myeloblastic or monoblastic leukemia. Auer rods which are eosinophilic cytoplasmic rods can be found in as many as 50 per cent of patients with myeloblastic leukemia and are probably pathognomonic for either myeloblastic or monoblastic leukemia.

DIFFERENTIAL diagnosis in acute leukemia involves a number of different hematologic syndromes such as aplastic anemia, agranulocytosis, idiopathic thrombocytopenic purpura and infectious mononucleosis. If the bone marrow is examined, however, there should be little confusion in making the diagnosis of acute leukemia. The only disease which presents much of a problem in the differential diagnosis is neuroblastoma, and it is confined largely to the pediatric age groups. A word should be said about leukemoid reactions and particularly the coincidence of tuberculosis and acute leukemia. There is no evidence that the incidence of leukemia is higher in patients with tuberculosis than it is in the general population. Nonetheless, the two diseases are frequently associated, and in occasional cases one may wonder whether tuberculosis is causing an atypical leukemoid reaction resembling acute leukemia. Unfortunately, there is no really good evidence that this has ever taken place, although the literature contains many suggestive cases.

I would like to discuss some of the common clinical problems that arise during the course of acute leukemia. The first is the occurrence of fever. This can be a very perplexing problem because sometimes, as exemplified by the patient presented this morning, extensive investigations yield no explanation for the fever. Fever occurring early in the course of acute leukemia is usually due to the disease itself and not to infection. However, as the disease progresses, fever is increasingly likely to be due to infection; and very unusual pathogens may be involved. It is important to do multiple cultures. A negative result of examination of the urine does not rule out the presence of a urinary tract infection, since the cellular response to infection can be so deficient in leukemic patients.

The second complication, hypercalcemia, is not at all as common as fever but I am mentioning it

merely to call it to your attention. Hypercalcemia is not nearly as frequent in acute leukemia as it is for example in multiple myeloma, but it has been reported with increasing frequency in recent years and we ourselves have seen one case in the last year.

Complications from abnormalities of uric acid metabolism are very frequent in patients with acute leukemia. Prodigious levels of serum uric acid may develop, resulting in deposition of urate in the tubules and in uric acid blockade of the kidney. This event can occur in at least two circumstances: shortly after the initiation of therapy, and when the leukocyte count is rising rapidly. The uric acid complications can usually be handled reasonably simply, first by the administration of large amounts of fluids, and second by keeping the urine alkaline. To this end we routinely give patients with acute leukemia sodium bicarbonate during the day and a small dose of acetazolamide (Diamox®) at night. We determine the urinary pH at least four times a day and try to maintain it between six and seven. Four-hydroxypyrazolo-(3,4-d) pyrimidine (Allopurinol®) may also be useful in difficult cases.

HYPOFIBRINOGENEMIA has been thought by some to be characteristic of acute promyelocytic leukemia, a variety of leukemia in which the predominant cell in the marrow is the promyelocyte rather than the blast. However, it is not possible clinically to differentiate between promyelocytic and myelocytic leukemia on any other basis; and, indeed, hypofibrinogenemia has been reported in many cases of acute myeloblastic leukemia. The cause of the hypofibrinogenemia is usually unclear. In some patients fibrinolysis has been demonstrated; in others, intravascular coagulation. In at least one reported case of acute myeloblastic leukemia, intravascular coagulation was successfully treated for a short period with heparinization.

The final problem for discussion is central nervous system leukemia. This develops, as I mentioned earlier, almost as a rule in patients who are successfully treated for acute leukemia, more frequently in acute lymphoblastic than in myeloblastic leukemia. The drugs that are commonly used for maintenance therapy, namely, methotrexate and 6-mercaptopurine, do not cross the blood-brain barrier to any extent. Consequently, the central nervous system can be a relatively immune reservoir for the development of leukemic cells.

Frequently, the symptoms of this complication are minimal. The most commonly reported symptom is headache, and unless the physician who is attending the patient is aware that it may stem from leukemic involvement of the central nervous system, he may attribute it to tension or sinusitis, or perhaps ignore it. Nausea and vomiting are the second most common symptoms. Involvement of the cranial nerves may occur, usually either the seventh or sixth cranial nerves. The point to bear in mind is that if a patient with acute leukemia has a persistent headache for a few days which cannot satisfactorily be explained, lumbar puncture is mandatory and will usually reveal an increase in pressure. In addition, increased protein is frequently seen, as well as an increased number of cells, which may be leukemic. Decreased sugar content is a somewhat less common feature. Patients who have central nervous system leukemia can be treated in a variety of ways, such as by x-ray therapy to the brain or by lumbar puncture alone. We have recently been treating all of our patients with central nervous system leukemia by intrathecal injection of methotrexate and have had excellent results. This brings us to a discussion of therapy in this disease.

The first type of therapy is supportive. Blood transfusions are used to correct anemia. Platelet transfusions can be of great help although in adults it is very difficult actually to raise levels of circulating platelets. Infections in children have been treated by transfusions of granulocytes, but this has not been a practical procedure for wide use, since it is so difficult to obtain adequate numbers of granulocytes. The drugs in common use are adrenal steroids: vincristin, which acts by mechanisms which are so far unexplained, methotrexate, a folic acid antagonist, 6-mercaptopurine, an anti-purine, and cyclophosphamide, an alkylating agent. Prednisone and vincristin, given separately, are the most effective drugs in producing a remission in children with acute lymphoblastic leukemia. They are almost as effective in acute lymphoblastic leukemia of adults. In acute myeloblastic leukemia, none of the drugs is very effective. Six-mercaptopurine appears to be the best of the drugs but even with this drug the remission rate is only about 15 per cent. There has been a good deal of discussion recently about the possibility that adrenal steroids might be contraindicated in patients with acute myeloblastic leukemia. The evidence for this is not compelling. In some instances steroids may be of

benefit. The combined use of drugs has been shown to bring remission in a higher proportion of cases. For example, in acute lymphoblastic leukemia of children the simultaneous use of prednisone and vincristin has given approximately an 80 per cent remission rate. In addition, it has been shown that maintenance therapy will lengthen a remission once it is achieved. The drugs that have been most effective in this regard are methotrexate and 6-mercaptopurine. The toxicity of these drugs is well known. As far as prednisone is concerned, it is of some interest that bleeding ulcers have been reported in patients with acute leukemia who are being treated with this drug, but this is not a frequent complication. Vincristin commonly causes peripheral neuropathy. Methotrexate may cause mucous membrane ulcers and marrow depression, while 6-mercaptopurine causes gastrointestinal distress and marrow depression. Of all these drugs, 6-mercaptopurine is most likely to cause jaundice, usually due to cholestatic hepatitis. Cyclophosphamide is a marrow depressant.

There are a variety of experimental programs which are being considered at the moment, including the simultaneous use of several of these drugs in very large oral or intravenous doses. It has been possible, using such a regimen, to obtain remission in as high as 40 per cent of patients with acute myeloblastic leukemia. Whether this will be of any practical utility remains to be shown.

The final question is: Does all this therapy really help the patient with acute leukemia? Are we doing anything beneficial when we treat patients with acute leukemia? I think you would agree that we probably are. The data of Freireich and Frei which was recorded in the *Journal of Chronic Disease* some years ago demonstrate the improvement in survival in patients with acute lymphocytic or myelocytic leukemia who have remissions. If a patient has a remission, his survival is prolonged over that of the patient who does not have a remission by about the duration of remission. This prolongation is not a very substantial one in most cases, however, and the course is almost inevitably tragic. One can only hope that some of the work that Dr. Cline is going to tell us about now will lead to more successful therapy of acute leukemia.

Etiologic Considerations

DR. MARTIN J. CLINE: The concept that a mutation in a hemopoietic cell line is responsible for

leukemia has been with us for about a quarter of a century. By mutation, I mean an acquired abnormality of genetic material as opposed to one that is inherited. As the discussion unfolds, you will see that the distinction between an acquired and an inherited abnormality may be a rather fuzzy one. What is the basis of this mutation theory? At first it was based on the observation that there was very little evidence for an inherited tendency in human leukemia. Subsequently it was shown that, in animals exposed to known mutagenic agents, there was an increased incidence of leukemia. Most conclusively, it has been shown recently that in virtually every case of human acute leukemia there are abnormalities of the chromosome patterns of the leukemic cells which are not found in the hemopoietic cells of near relatives. These chromosomal abnormalities are either aneuploidy, polyploidy or structurally abnormal chromosomes.

If leukemia is a mutation, the questions that can logically be asked are: What are the known mutagenic agents and what is the evidence implicating each of these in acute leukemia? The known mutagenic agents can be simply summarized. These are ionizing irradiation, chemical mutagens and viruses. I would like to examine the evidence implicating each of these in acute leukemia.

Let us first examine radiation leukemogenesis. It is well known that ionizing irradiation can induce alterations in deoxyribonucleic acid (DNA). It can produce breaks in the DNA chain or cross-linking of the twin strands of the DNA molecule. In bacterial systems, ionizing irradiation increases the incidence of mutation; irradiation can produce murine leukemia.

Most pertinent to this discussion perhaps is the epidemiologic evidence implicating radiation in leukemogenesis in man. The great bulk of the evidence in this area has been accumulated from the studies of the survivors of the bombing in Hiroshima. Important information has been gained from these studies. First of all, above a dose of approximately 80 rads, there appears to be a linear increase in the incidence of leukemia with an increase in the dose of radiation. A person who was standing approximately a thousand meters from ground zero at the time of the detonation subsequently had a 30-fold increase in the likelihood that leukemia would develop. The closer he approached the hypocenter, the greater were the chances that leukemia would develop.

The second important point that emerged from these studies was the observation that there is a latent period between exposure to ionizing radiation and the development of leukemia. This period varied between two and 15 years but the greatest incidence was at about six years, or in 1951. Another fact that emerged was that the morphologic type of leukemia that subsequently developed appeared to be related to the age of the victim at the time of exposure: In children, lymphoblastic leukemia developed; in adults, myeloblastic leukemia.

The evidence obtained from the other studies all tends to support the evidence acquired from the studies in Hiroshima. These include: leukemia in children previously exposed to thymic irradiation, leukemia in patients treated with Iodine¹³¹ for hyperthyroidism or by radiation of the spine for ankylosing spondylitis, the more controversial studies of increased incidence of leukemia in children after exposure to intrauterine irradiation, and the increased incidence of leukemia in radiologists. There are more than 300 well-documented reported cases of leukemia associated with excessive exposure to ionizing radiation.

ONE MAY LOGICALLY ASK whether radiation works directly or by way of an intermediate. It is known in bacterial systems at least that radiation can activate lysogenic viruses—that is, bacteriophage which is present in the bacterial cell but which is essentially dormant. The viral genetic information is present but it is not expressed until it is activated by ionizing radiation. At that time, the bacteriophage replicate and destroy the host cell. There is at least one analogy for this situation in mammalian systems. In certain strains of mice in which leukemia is induced by ionizing irradiation, the leukemia may be subsequently transmitted by a cell-free filtrate, or presumably by a virus. It should be noted that in bacterial systems at least the genetic information of the lysogenic virus may be transmitted along with the host cells' DNA; thus the distinction between an inherited and an acquired anomaly may be difficult.

The evidence for chemical leukemogenesis is less secure. Chemically induced alterations in DNA are known and certain agents are capable of producing mutations in bacterial systems. It is known that methylcholanthrene can produce leukemia in certain strains of mice, but the epidemiologic evidence implicating chemicals in acquired leukemia

in man is not so strong. Such evidence as exists is based largely on the observation that in many persons who have had long exposure to benzene, first aplastic anemia will develop and then, after a latent period of years, leukemia. Reports of this phenomenon have been largely from the Italian literature.

Since the observation by Gross in 1951 that a mouse leukemia could be transmitted by a cell-free filtrate, the viral theory of leukemogenesis has been increasingly exercised. Supporting evidence for such a theory can be divided into five categories: (1) the analogy with virus-associated animal leukemia, (2) the sporadic outbreaks of human leukemia, (3) the rather interesting evidence obtained in Burkitt's lymphoma, (4) the reported observation of virus-like particles in the blood of leukemic patients and (5) the rather controversial reports of isolation of these viruses. I should like to discuss each of these categories.

First of all, the mouse leukemias. In 1941, Cole and Furth described a mouse strain with a high incidence of spontaneous leukemia. As I have noted, a decade later Gross showed that this leukemia was due to a virus. Among the important facts that have subsequently emerged from the study of these leukemias are the following observations: After inoculation of the susceptible mouse with a virus, there is a latent period of months before the development of leukemia. During this period it can be shown that the thymus gland is the principal and primary site of proliferation of the virus. It is interesting that thymectomy also decreases the incidence of leukemia induced in certain mice by chemicals and by exposure to radiation, suggesting that a virus may be involved in these situations as well. It has been shown that the isolated nucleic acids of these viruses alone can increase the incidence of leukemia in susceptible mice. The story for avian leukemia is in essence quite similar to that for the rodent leukemia, and I won't discuss these in any detail. But I will note that as early as 1908 it was suggested that there might be an association of a virus with avian leukemia.

Sporadic outbreaks of human leukemia have been reported since 1923. The most recent and best studied of these occurred in a small parish in Niles, Illinois. Eight cases were involved. The most important observation implicating a transmissible agent such as a virus was the finding of antibodies to leukemic antigens in the parents and

siblings of patients. Such antibodies were not found in a control population.

Burkitt's lymphoma is an exceedingly interesting disease entity which may be related to the problem of viral leukemogenesis and tumorigenesis. It is a lymphoma with characteristic clinical and pathological features and it may occasionally involve the circulating blood. One of its most interesting features is its geographical distribution. It is found almost exclusively in a band across the tropical area of Africa, from Kenya and Tanganyika in the east to Dakar in the west. It is found in altitudes variously reported as 3,000 to 5,000 feet. In Africa, it accounts for some 50 to 70 per cent of all malignant disease in children. But it is not a disease of African children alone. It is a disease of children in Africa; that is to say, Europeans, Berbers and other racial groups living in this area are also affected by the disease. On the basis of its distribution in a hot, moist, tropical area and at low altitudes it has been suggested that an arthropod vector may be involved, and recently there have been claims for the isolation of a filtrable agent from the serum of patients with this lymphoma.

It is quite clear that in the blood of some patients with acute leukemia there are particles which resemble those which have been described in the rodent leukemias. In their initial studies Dalton and his colleagues at the National Institutes of Health found such particles in some seven of 50 patients. Kresley at Oakridge found them in the majority of leukemic patients.

The questions that could logically be asked at this point are: Are these particles viruses? And if they are viruses, are they etiologically related to leukemia? The question of whether they are viruses cannot be answered definitely at present. As to their etiologic relationship to leukemia, there are two schools of thought. One, which we might call the predestination school, believes the leukemic cell is going to become leukemic anyway and happens to be a good culture medium for passing viruses. The activist school believes that these viruses are leukemogenic. Neither group has incontrovertible evidence.

Can these agents be cultured? There are many reports of failures and few of successes. The early reports of successes have now been opened to question since the demonstration that the agents involved were in fact not viruses but were myco-

plasma; that is, agents like the Eaton agent that cause primary atypical pneumonia. These are the smallest of free-living organisms. They are somewhere in the evolutionary chain between viruses and bacteria and have many of the characteristics of viruses. Whether they are etiologic in leukemia is moot. At least we know that they do cause one human disease.

There is one other bit of evidence that viruses may be leukemogenic in man—evidence that is acceptable at least to virologists. Material isolated from patients with lymphoblastic leukemia and from Burkitt's lymphoma can interfere with the proliferation of other viruses in tissue culture.

If viruses are leukemogenic, how do they induce mutation and how do they alter cell metabolism? Well, the tumorigenic viruses in mammals as opposed to leukemogenic viruses are all DNA viruses, sv 40, polyoma, and some of the adeno viruses. These can induce chromosomal breaks similar to those I have shown. They have the interesting characteristic that after infection they appear to disappear from the cell. Their antigens can be found and the malignant transformation persists but the viruses are no longer present. In contrast, in avian and murine leukemia, the viruses involved are ribonucleic acid (RNA) viruses. These viruses stay around and can infect new host cells. The alterations in the cell's economy which can be induced by such viruses can be briefly summarized. The DNA and RNA viruses essentially act by interfering with transcription of the host DNA, so that the host messenger, RNA, is no longer formed. Instead, viral messenger RNA is made, and viral proteins are made, including the enzymes necessary for the synthesis of specific viral genetic material. In essence, then, the virus subverts the cell's economy for its own purposes.

What are the prospects in therapy if viruses are etiologic in leukemia? First of all, one may consider attempting to interfere with cell infection either with interferon, by specific vaccination, by chemical means or by viral means. Included in our list of references is a paper¹ that describes the use of viral agents to treat acute leukemia. However, if the viruses involved are DNA viruses and disappear from the cell after inducing leukemia, then suppressing infection is a little like locking the barn after the horse is gone. It may be more rational therefore to attempt to interfere selectively with the acquired biochemical aberrations of the leukemic cell, and this to some extent is the

rationale of present day chemotherapy. And lastly, there is the concept of introduction of new genetic material. This is quite feasible in vitro. It has been shown that if one isolates liver RNA and adds it to a culture of Hela cells, the Hela cells will then make albumin like the liver. There has already been one trial of the use of normal RNA instilled in the sternal marrow of a leukemic patient with the claim that there was a subsequent normal differentiation of the leukemic cells.

In summary, the evidence is exciting and intriguing, but by no means conclusive, that viruses are leukemogenic in man. The principal problems to be resolved are the isolation of specific viral agents which can be shown to be cytopathic for mammalian tissue culture material, and then the induction of leukemia by such agents in experimental animals. We have a long way to go before we fulfill Koch's postulates.

EDITOR'S NOTE: Shortly after presentation of this case, the patient was treated with a combination of prednisone, 6-mercaptopurine, vincristin and methotrexate. A complete hematological remission ensued. At present, six months later, the patient is on a regimen in which 6-mercaptopurine is alternated every four to six weeks with methotrexate. He is in complete remission.

ACUTE LEUKEMIA

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